IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/691,033
Applicant	:	Zongqin Xia, et al.
Filed	:	October 21, 2003
Art Unit	:	1654
Examiner	:	Susan D. Coe
Title	:	SMILAGENIN AND ITS USE
Docket No.:	:	HASEL-65949
Customer No.	:	24201

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Daryl Rees, hereby declare as follows:

1. This Declaration supplements the Declaration I have previously provided in this matter.

2. This Declaration relates to the objections raised in the Office Action dated 29 August 2005, which I have reviewed, and the matters discussed at the interview that I attended with Examiner Coe on March 8, 2006.

3. In the Office Action dated 29 August 2005, Examiner Coe argued that, while *in vitro* cell cultures and rat models "may be effective for screening possible anti-Parkinson's candidates, these models are not necessarily predicative of results in human patients".

4. Examiner Coe further argued that:

> "the art teaches that effective treatment of Parkinson's disease in rat models does not necessarily predict successful treatment in humans due

to differences between the species. The art recommends using primate models as the most clinically relevant model for predicting successful treatment in humans (see Eberling et al. Experimental Neurology (2002), vol. 178, pp. 236-242, specifically page 240, first column and Emborg; Journal of Neuroscience methods (2004), vol. 139, pp. 121-143, specifically page 134, first column). In order to test the effectiveness of Parkinson's treatments, Eberling and Emborg indicate that non-human primates should be used as animal models after testing has been performed on rat models. Applicant does not perform any testing on humans or non-human primates; thus, a person of ordinary skill in the art would be forced to carry out further testing to determine if the smilagenin is actually able to treat Parkinson's disease in humans as claimed."

5. In this Declaration I will explain that in my expert opinion Examiner Coe, despite her obvious knowledge of the art, is confusing the requirements in the art for **preparing a therapeutic agent for clinical trials** with the requirements in the art for **reasonably predicting human activity**. In my expert opinion, Examiner Coe is also overlooking the substantial difference made by the fact that the present invention relates to a **non-toxic, lipophilic, relatively small, molecule**, in contrast to the **proteins and other large or macromolecules** typically of interest as agents for treating Parkinson's disease.

6. I start firstly by challenging Examiner Coe's implication that models that are "effective for screening possible anti-Parkinson's candidates" can still be insufficient to support a patent application for treatment of Parkinson's disease. The whole point of a screen for possible anti-Parkinson's candidates is to identify **compounds for which a credible prediction of biological activity relevant to the treatment or prevention of Parkinson's disease can be made.** If the screen could not do that, it would be useless as a screen for possible anti-Parkinson's candidates.

Therefore, to me it follows logically that screen data should in principle provide a sufficient basis for the filing of a patent application. I am advised, and can believe, that there is no rule of law in the US or any other Patent Office, that says that a patent for a newly invented medical treatment must include any particular type of test data. It is my understanding that the essential requirement is that a patent should disclose enough information that the credibility of the claimed treatment is established to the reader, who is presumed to have skill in the art.

On this basis, it seems to me that Examiner Coe may be arguing from an essentially illogical position.

Nevertheless, I will now deal in detail with Examiner Coe's apparent belief that only primate or human models can be predictive of activity at treating Parkinson's disease.

7. It is convenient to start at the part of Emborg specifically cited by Examiner Coe, namely page 134, first column.

The discussion starts ("Results", paragraph 1) with a statement that "ideally, the administration of a neuroprotective agent prevents the behavioural impairment, neurochemical deficits and pathologic degeneration characteristic of the model". There is a cross-reference to publications relating to the naturally occurring protein glial derived neurotrophic factor (GDNF), which is currently in trials as a potential anti-Parkinsonism agent.

Emborg then cautions that – **similarly to clinical assessment of neuroprotection** – several factors can confound the results in animal models and have to be accounted for. It states that "careful experimental design and use of multiple outcome measures with clinical relevance facilitate the interpretation of the data", which is a rather complicated way of saying that one should not place all one's reliance on one test, but should look for neuroprotective activity across a range of tests.

I agree with all of this, but do not see that it supports what Examiner Coe argues. On the contrary, it seems that Emborg is taking the perfectly reasonable approach that the tests used should detect **neuroprotective action** of the agent and that one should use a **range** of tests. Emborg also makes the useful point that clinical assessment of neuroprotection is as open to confounding factors as animal models.

As an aside, it is important to understand that Emborg is being objective as to the advantages and disadvantages of the various accepted animal models. For example, at pages 125 to 126, it reviews the animals used and their characteristics. Rodent models and their advantages are described. The essential role of the primate models to **"bridge the gap"** (page 125, column 2, line 38) between rodent models and clinical trials on humans is described.

The reality, however, is that clinical trials for neuroprotective strategies should be based on a general picture of activity built up over a number of tests (see Emborg, Figure 2).

According to Emborg's Figure 2, **rodent models are highly predictive of the eventually proven human effectiveness**. Figure 2 is based on activity being shown in the (earlier) rodent models as well as the final human trials. (Agents that show no activity in the rodent models will not be put forward for the final human trials, so we have no way of knowing how many good treatments of Parkinson's disease have been lost to mankind in this way.)

8. On page 134, column 1, Emborg then goes on to say that evidence of neuroprotection in rodents does not ensure similar results in non-human primate models, probably due to monkeys' bigger volume distribution and complexity of the central nervous system (CNS).

All this is saying is that on occasions Figure 2 can break down, or at least the picture can becomes confused, at the monkey test stage, but that there are reasons for this.

Emborg refers by way of example to publications showing that, in the case of the non-immunosuppressive immunophilin ligand GPI-1046, i.e. 3-(3-pyridyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate, translation to Parkinson's patients may prove even more difficult. One of the publications referred to is Eberling.

As stated in the Abstract, Eberling examined the neuroregenerative effect of GPI-1046 in MPTP-treated monkeys (as a model of Parkinson's disease) in view of the known effect of the agent to **regenerate dopamine cells in association with functional recovery** in rodent models.

Eberling says that GPI-1046 does not have **neuroregenerative** effects in MPTP-treated monkeys (Eberling, title)

However, Eberling is careful not to rule out that GPI-1046 may have efficacy in primates or humans. Thus, in the "Discussion" section, pages 240 to 241 (page 241, column 1, lines 11 to 20), he comments (emphasis added):

> "In primates, while we did not observe any evidence of **neuroregeneration**, the previous report of Emborg et al [a study in 2001] suggested the possibility of **neuroprotection** since the number of TH-positive nigral neurons appeared to be unchanged following concurrent treatment with MPTP and GPI-1046 in individual animals. The majority of the animals, however, did not show evidence of neuroprotection, and **the mechanism of any protective effects in the MPTP models remains to be established.**"

From this I take the teaching that the MPTP models – in both rodents and primates – are problematic because the mode of action of neuroprotection in any MPTP-challenged animal is not yet established. It must be remembered here that MPTP is a neurotoxin which is administered to the chosen animal model and is **not present** in the bodies of human Parkinson's disease patients.

It is tempting to the casual observer, but wrong, to read more into this type of reference than it can bear. Similarly, it is wrong to oversimplify test results and to ignore that the life processes and their disorders are incredibly complex

phenomena, the exploration of which inevitably throws up a complex and sometimes contradictory pattern of data, through which a clearer understanding and knowledge only slowly and painstakingly evolves.

Eberling has reported one finding in the complex endeavour of many workers to understand and treat Parkinson's disease and other neurodegeneration using the best tools available within the perfectly proper legal and ethical constraints. Far from ruling out that GPI-1046 may have efficacy in primates or humans, Eberling carefully considers (page 214, from column 1, line 21 onwards) possibilities for why GPI-1046 could potentially be effective in primates yet its experiment simply failed to show it. This is not, to my mind, the approach to be expected of someone who gives no credence to test results using rodent models of neurodegeneration, and it is my firm opinion that Eberling – like all workers in this field, including myself – gives proper weight to test data obtained in any appropriate model of neurodegeneration. Indeed, it is precisely because of the positive results of GPI-1046 in the rodent models that the work on primate models of Parkinson's disease was attempted at all!

9. So, Emborg is saying is that sometimes Figure 2 breaks down, or at least becomes confused, if the test strategy uses a monkey test stage, but that there are reasons for this, and GPI-1046 seems to be an example of this. It is also saying that the rodent models are inherently credible and that compounds that perform on those models can be considered as having established a believable activity against Parkinson's disease.

GPI-1046 is a non-immunosuppressive immunophilin ligand. Immunophilins are intracellular proteins which are receptors for predominantly immunosuppressive drugs, although a few non-immunosuppressive immunophilin ligands such as GPI-1046 have recently been identified.

However, all our research suggests that smilagenin is not an immunosuppressant, does not behave as an immunophilin ligand, does not exert its powerful neuroprotective and neuroregenerative effects via immunophilin ligandic binding and in general cannot be compared with immunophilin ligands.

Therefore, there is no reason to suppose that Figure 2 will break down or become confused in the case of smilagenin, and good reasons to suppose that it will not.

10. Returning to Emborg, page 134, it goes on to make the important point that "the biological properties of the putative neuroprotective agent and the chosen method of delivery have an impact on the strategy success".

The cited example of this is the protein GDNF mentioned earlier.

However, smilagenin, the agent of the present invention, is not GDNF and is not similar to it or any other protein either. Smilagenin does not behave like any protein according to our knowledge. Therefore, again there is no reason from GDNF to suppose that Figure 2 will break down or become confused in the case of smilagenin.

11. It is true that the assessment of 'protein drugs' in a laboratory rodent model may not be the most appropriate, because of the high likelihood of immune rejection or other toxicity of the 'protein drug' before it enters the brain. The human system can sometimes in that case be modelled better by use of a primate test animal. Smilagenin, the active in the present invention, is a steroidal spirostane sapogenin. This type of molecule is very different from proteins. It is much smaller, is non-toxic, lipophilic and non-immunogenic, so that in the present case non-primate test systems are entirely appropriate. It is likely that a primate model will in fact not be required to "bridge the gap" – as Emborg puts it – as a preliminary to clinical trials.

12. As mentioned in my previous Declaration, I am Chairman of the Huntingdon Research Ethics Committee in the UK. I am therefore well acquainted with ethical issues surrounding animal testing of candidate pharmaceuticals. It is my firm opinion that it would be unethical, for supporting a patent filing, to test a small, non-toxic, non-protein, lipophilic molecule like smilagenin on a primate (e.g. an MPTP or 6-hydroxydopamine challenged monkey) for activity against Parkinson's disease. To do so would involve unnecessary suffering to the animal, which would not be outweighed by any pre-clinical data that might be obtained from such tests, as pre-clinical data of equivalent or higher worth could equally well be obtained from cell and rodent systems.

13. Based on the forgoing, I strongly consider that Examiner Coe's continued objection to this application is unwarranted, and I request allowance on the basis of the current claims.

I hereby state that the foregoing is true and correct to the best of my knowledge, and that all statements of fact are based on personal knowledge and/or reasonable investigation.

12th May 2006

Dated

Daryl Rees